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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/125,005	07/30/98	CAPUT D	IVD-913

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PATENT DEPARTMENT
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EXAMINER	
UNGAR, S	
ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 10/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/125,005	Appl[illegible]s) Caput et al
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Aug 11, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-38* is/are pending in the application.

Of the above, claim(s) *6-32 and 35-38* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 33, and 34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 1

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed August 11, 2000 (Paper No. 11) in response to the Office Action of April 12, 2000 (Paper No. 9) is acknowledged and has been entered. Claims 1-38 are pending in the application. Claims 6-32 and 35-38 have been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to non-elected inventions. Claims 1-5 and 33-34 are currently under prosecution.

2. The response (Paper No. 11) to the restriction requirement of April 12, 2000 has been received. Applicant has elected Group III, claims 1-6, 25 and 33-36 drawn to SEQ ID NO:6 for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a). It is noted that claims 6 and 25 have been withdrawn from consideration because claims 6 and 25 were not included in Group III in the restriction requirement of April 12, 2000 for the reasons previously set forth.

3. It is noted that the application claims priority to French Patent No. 96 01309. However, no priority document has been received. Without the priority document Examiner has established a priority date for the instantly claimed invention of February 3, 1997.

4. Upon review and reconsideration, restriction to one of the following inventions is required under 35 U.S.C. § 121:

Group I. Claims 1-5 and 33-34 are drawn to a polypeptide of SEQ ID NO:6 classified in Class 530, subclass 350.

Group II. Claims 35-36 are drawn to inhibitors of SR-p70 activity classified in Class 530, subclass 300+.

5. The inventions are distinct, each from the other because of the following reasons:

Inventions I-II as disclosed are biologically and chemically distinct, unrelated in structure and function, made by and used in different methods and are therefore distinct inventions.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. A telephone call was made to Paul Dupont (610)-889-6338, on October 23, 2000 to request an oral election to the above restriction requirement. Mr. Dupont made an oral election to the above restriction requirement, a provisional election was made to prosecute the invention of Group I, claims 1-5 and 33-34. Affirmation of this election must be made by applicant in responding to this Office action.

Specification

8. Informalities where drawings are labeled, for example, Fig. 1 and Fig. 1 cont. rather than Fig. 1A and Fig. 1B are too numerous to mention. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where on the drawings these informalities may be found. Furthermore the Brief Description of the Drawings and all references to

the drawings in the specification must be amended to reflect the new numbering of the drawings. Appropriate correction is required.

9. The heading for the drawing section in the specification is not appropriate. The section must be labeled "Brief Description of the Drawings".

It is noted that the following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
© Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CAR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CAR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.

(l) Sequence Listing (see 37 CAR 1.821-1.825).
Appropriate correction is required.

10. Informalities where the Brief Description of the Drawings does not indicate which sequence on the drawings is identified, as for example SEQ ID NO:1 and SEQ ID NO:43 as described for Figure 1, are too numerous to mention. The Brief Description of the Drawings must describe and identify each sequence of the drawings. Appropriate correction is required.

11. The Brief Description of Figure 9 does not describe the figure as presented. The Brief Description describes (a and b), (a), (a and c), however, these labels are not found in Figure 9. Appropriate correction is required.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

13. Claims 1-5 and 33-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific asserted utility, a well established utility or a substantial utility.

The disclosed utilities for SEQ ID NO:6 or biologically active fragments thereof include prophylactic, therapeutic and diagnostic applications of these sequences, in particular in the field of pathologies linked to the phenomena of apoptosis or of cell transformation (p. 1, lines 5-10). However, neither the

specification nor any art of record teaches what SEQ ID NO:6 is, what it does do, they do not teach a utility for any of the fragments claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for SEQ ID NO:6, such as production of antibodies (p. 14, lines 31-39) apply to many unrelated polypeptide structures sequences. Additional disclosed utilities for SEQ ID NO:6 include therapy and diagnosis of conditions and diseases characterized by expression of SEQ ID NO:6 and for the production and characterization of activators and inhibitors of SEQ ID NO:6. The asserted utility of the SEQ ID NO:6 is based on the assertion that (SEQ ID NO:6) has structural homology to the tumor suppressor p53. In particular, the specification teaches that SEQ ID NO:6, SR-p70, is related to the p53 tumor-suppressing gene whose the antitumor activity of which is linked to its transcription factor activity (p. 1, lines 15-24). Because of the relationship to p53, the compositions of the invention afford a novel approach to treating the phenomena of carcinogenesis at the level of the control of multiplication and cell differentiation (p. 16, lines 12-14). The specification teaches that the structural homology between the DNA-binding domain of p53 and the central region of the SR-p70 enables it to be inferred that SR-p70 is a transcription factor. P53 consists of several functional domains, the N-terminal region (1-91) is involved in the activation of transcription and contains sites for interaction with different cellular and viral proteins, the central portion, (amino acids 92-292) permits binding to the specific DNA sequences located in the promoter regions of certain genes and also possesses numerous sites for interaction with viral proteins which inhibit its activity and the last 100 amino acids of

p53 are responsible for its oligomerization as well as for the regulation of its oligomerization. (P. 45, lines 5-23). The sequence homology between p53 and SR-p70 is significant in particular as regards the amino acids involved directly in the interaction with DNA suggesting that SR-p70 binds to the p53 sites on DNA. From this homology, it may be deduced that the SR-p70 protein exerts a control over the activity of the genes regulated by p53 (p. 45, lines 24-35). Consequently, like p53, SR-p70 gene must be involved in the control and regulation of the cell cycle (paragraph bridging pages 46-47). However, it is well known in the art that there are a multitude of DNA binding proteins, thus the function of DNA binding is one shared by a multitude of proteins and is not specific to SEQ ID NO:6.

In addition, contrary to the assertions of the specification, it is not possible to determine from the information provided that SEQ ID NO:6 is a transcription factor or that it is involved in the control of the activity of the genes regulated by p53. A review of the literature has revealed an identity between SEQ ID NO:6 and p53 proteins ranging from 25.2 % to 17.7% (see attached page 1 of database sequence search us-09-125-005-6.rsp) and has revealed, as taught by the instant specification, that the predominant area of homology rests between amino acids 101 and 280 of SEQ ID NO:6. A review, for example, of the ovine p53 of Dequiedt et al (DNA Seq, 1995, 5:255-259, database sequence search us-09-125-005-6.rsp, result 7) reveals that the identity of the two proteins in the region 101 through 280 is 64%. In the instant example, the overall identity between SEQ ID NO:6 and the protein of Dequiedt et al is 22.3%. It is clear that although there is an overall identity of 22.3%, there is also an overall dissimilarity of 77.7%. Even in the putative DNA binding

domain there is a 36% dissimilarity in amino acid constitution. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological

activity and characteristics of a protein. Clearly, with 77.7% dissimilarity, to p53 overall and a 36% dissimilarity to p53 in the putative DNA binding region, the function of the SEQ ID NO:6 polypeptide could not be predicted, based on sequence similarity with p53, nor would it be expected to be the same as that of p53. It is very clear, given the teaching of the specification that the DNA binding domain of p53 permits binding to the specific DNA sequences located in the promoter regions of certain genes and that the N terminal domain is involved in the activation of transcription and contains sites for interaction with different cellular and viral proteins and that the C terminal domain is involved with oligomerization and regulation of oligomerization. It cannot be predicted, based upon the information known in the art, what effect changes in 36% of the DNA binding domain proteins will have upon DNA binding sites and what effect changes of 77% overall will have on the function and activity of the protein . In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than

30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 77.7 % overall dissimilarity to p53 and with 36% dissimilarity in the putative DNA binding region, the function of the SEQ ID NO:6 polypeptide could not be predicted, based on sequence similarity with p53, nor would it be expected to be the same as that of p53. Further, the specification specifically admits on the record that the biological function of SR-p70 is unknown (p. 47, lines 34-36). Even if the polypeptide of SEQ ID NO:6 is a DNA binding protein, neither the specification nor any art of record teaches what the

polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or would function contemplated. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptides. Additional experimentation is required to further characterize SEQ ID NO:6 in order to determine a utility and therefore the sequence does not have a substantial utility. Because the claimed invention is not supported by a specific utility, a well established utility or a substantial utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

15. Claims 1-5 and 33-34 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a specific utility, a well established utility, a substantial utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

In the event that Applicants might be able to overcome the 35 USC 101 and 112, first paragraph rejections above, claims 1-5 and 33-34 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a composition comprising SEQ ID NO:6, does not reasonably provide enablement for polypeptides comprising a biologically active fragment of SEQ ID NO:6 derived from SEQ ID NO:6 or a polypeptide comprising a sequence selected from SEQ ID NO:6. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to a biologically active sequence derived from SEQ ID NO:6 and a polypeptide comprising a polypeptide comprising an amino acid sequence selected from SEQ ID NO:6. This includes a polypeptide comprising any fragment derivatized in any way by "mutation deletion, addition substitution and/or chemical modification of amino acids and any polypeptide comprising an amino acid sequence selected from SEQ ID NO:6 which reads on any polypeptide comprising even two consecutive amino acids identical to those recited in SEQ ID NO:6. The specification teaches that biologically active is defined as capable of binding to DNA and/or exerting transcription factor activity and/or of participating in the control of the cell cycle, or differentiation and of apoptosis and/or capable of being recognized by the antibodies specific for the polypeptide of SEQ ID NO:6 and capable of inducing antibodies which recognize this polypeptide (p. 3, lines 29-37). One cannot extrapolate the teaching of the specification to the scope of the claims because, as drawn to biologically active fragments, it cannot be determined from the

specification which domains are capable of functioning as defined by the specification. Given, the information in the specification, there is no way to determine whether or which sequences are involved in exerting transcription factor activity, participating in the control of the cell cycle or differentiation or apoptosis. Further, it cannot be determined which fragments would be capable of being recognized by antibodies specific for SEQ ID NO:6 or capable of inducing antibodies which recognize this polypeptide. For example, it is well known in the art that it cannot be predicted, based on primary amino acid sequences which fragments can be used to produce synthetic amino acid sequences as immunogens to develop antibodies. One cannot be certain how well exposed such a peptide is nor how immunogenic it is. Furthermore, this does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Although it is clear, as disclosed above, that the putative DNA binding domain has a 64% homology to the DNA binding domain of p53, it is not clear, given the teachings of Bowie, *Supra*, Burgess et al, *Supra*, Lazar et al, *Supra* and Bork, *Supra* that this area of homology is actually a DNA binding domain. Further, there is no teaching of how to make biologically active fragments that are derived from SEQ ID NO:6 that will function as claimed. As drawn to the claimed polypeptides comprising a/an amino acid sequence of SEQ ID NO:6, the claims clearly encompass polypeptides comprising non-disclosed amino acid sequences attached to the polypeptide of SEQ ID NO:6.

Clearly, it would be expected that a substantial number of the polypeptides encompassed by the claims **would not** share either structural or functional properties with the polypeptide of SEQ ID NO:6. The specification fails to provide an enabling disclosure for how one would use such polypeptides. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to make or use the claimed fragments with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. Claims 33 and 34 are rejected under 35 U.S.C: 112, first paragraph, because the specification, while being enabling for a composition comprising SEQ ID NO:6 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a pharmaceutical composition comprising the polypeptide of Claim 1 or a polypeptide comprising a polypeptide comprising an amino acid sequence of SEQ ID NO:6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a pharmaceutical composition comprising the polypeptide of Claim 1 or a polypeptide comprising a polypeptide comprising an amino acid sequence of SEQ ID NO:6. This includes a composition comprising a polypeptide comprising a biologically active fragment of SEQ ID NO:6 or a polypeptide comprising two sequential amino acids identical to those in SEQ ID

NO:6. The specification teaches that the invention relates to therapeutic applications of the sequence in the field of apoptosis or of cell transformation (p. 1, lines 5-9). One cannot extrapolate the teaching of the specification to the scope of the claims because inherent to pharmaceutical compositions is an *in vivo* use thereof. The specification does not provide guidance by way of general methods or working examples which teach the feasibility of *in vivo* use for the claimed polypeptide. It is clear that the invention is drawn to therapeutic applications of the sequence in the field of apoptosis or of cell transformation. It is well known in the art that these two parameters are of paramount importance in the treatment of cancer. Thus, it appears that the claimed pharmaceutical compositions read on compositions for the treatment of cancer. However, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept an assertion that the claimed pharmaceutical composition could be used for therapeutic applications of the sequence in the field of apoptosis or of cell transformation. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into

uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed pharmaceutical composition could be used for therapeutic applications of the sequence in the field of apoptosis or of cell transformation. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain, *Supra*, specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). There is no teaching in the specification that the pharmaceutical composition claimed is selective for tumor cells

or that the claimed composition would act only on dividing cells. In addition, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the composition. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the composition has no effect, circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed pharmaceutical compositions with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to use the claimed invention.

17. Claims 1-5 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:6 and therefore the written description is not commensurate in scope with the claims drawn to polypeptides comprising a biologically active fragment of SEQ ID NO:6 derived from SEQ ID NO:6 or a polypeptide comprising a sequence selected from SEQ ID NO:6.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Although drawn to the nucleic acid art the findings of *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 are clearly relevant to the instant invention. *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 found that adequate written description requires more than a mere statement that it (a nucleic acid) is part of the invention. The nucleic acid itself is required. See

Furthermore, although again drawn to the nucleic acid art, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court

indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by derivatizing the polypeptides of the invention and specifically teaches that a derivative is any variant of SEQ ID NO:6 or any molecule resulting from a modification of a genetic and/or chemical nature of SEQ ID NO:6, that is by mutation, deletion, addition, substitution and/or chemical modification (p. 3). There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill

would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a single polypeptide sequences and a general teaching of the definition of derivatization, is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated polypeptide comprising SEQ ID NO:6, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

18. Claims 4 and 33-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in the recitation of the phrase "a corresponding gene". The claim is confusing because it is not clear what a corresponding gene is.

Claims 33 and 34 are indefinite because claim 33 recites the phrase "an effective amount". The phrase "an effective amount" is indefinite when the claims fail to state the funciton which is to be achieved. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1-4 and 33-34 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dequiedt et al (DNA SEQ, 1995, 5:255-259, see enclosed Database Search, us-09-125-005-6.rsp, result 7).

It is noted that the preamble recitation of pharmaceutical composition is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient *per se*, which is a polypeptide comrpsing SEQ ID NO:6.

It is noted that the patentability of a product-by-process claim, Claim 4, is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985).

It is noted that a polypeptide comprising SEQ ID NO:6 includes any polypeptide comprising any biologically active fragment or derivative of this polypeptide (p. 3, lines 4-9)) and that a biologically active fragment is defined in the specification as being capable of binding to DNA and/or exerting transcription factor activity and/or of participating in the control of the cell cycle, or differentiation and of apoptosis and/or capable of being recognized by the antibodies specific for the

polypeptide of SEQ ID NO:6 and capable of inducing antibodies which recognize this polypeptide (p. 3, lines 29-37)

The claims are drawn to a purified polypeptide comprising SEQ ID NO:6, comprising any biologically active fragment of SEQ ID NO:6, comprising a sequence lying between residues 110-310 of SEQ ID NO:6 (which reads on two consecutive amino acids), comprising a polypeptide comprising a sequence of SEQ ID NO:6 (which also reads on two consecutive amino acids).

Dequiedt et al teach a p53 polypeptide which is a derivative of SEQ ID NO:6, as defined by the specification, which comprises a DNA binding domain, comprises numerous sequences identical to those of SEQ ID NO:6 in the region between residues 110-310 ranging from two to ten consecutive amino acids (see us-09-125-005-6, result 7).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed

invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

22. Claims 1 and 5 are rejected under 35 U.S.C. § 103 as being unpatentable over Dequiedt et al (DNA SEQ, 1995, 5:255-259, see enclosed Database Search, us-09-125-005-6, result 7). in view of US Patent No. 5,532,348.

It is noted that a polypeptide comprising SEQ ID NO:6 includes any a polypeptide comprising any biologically active fragment or derivative of this polypeptide (p. 3, lines 4-9)) and that a biologically active fragment is defined in the specification as being capable of binding to DNA and/or exerting transcription factor activity and/or of participating in the control of the cell cycle, or differentiation and of apoptosis and/or capable of being recognized by the antibodies specific for the polypeptide of SEQ ID NO:6 and capable of inducing antibodies which recognize this polypeptide (p. 3, lines 29-37)

The claims are drawn to a purified polypeptide comprising SEQ ID NO:6, comprising any biologically active fragment of SEQ ID NO:6 wherein the polypeptide is a recombinant polypeptide produced in the form of a fusion protein.

Dequiedt et al teach as set forth above but do not teach the p53 protein in the form of a fusion protein.

US Patent No. 5,532,348 teaches a p53-GST fusion polypeptide (co; 5, lines 65-67) and a method of purifying the polypeptide by absorption onto glutathione sepharose beads (sentence bridging cols 5 and 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the polynucleotide encoding the p53 protein of Dequiedt et al for the polynucleotide encoding the p53 protein product of US Patent No. 5,532,348 and to produce a p53-GST fusion polypeptide using conventional methods in order to optimize the manufacture and purification of the p53 product. One of ordinary skill in the art would have been motivated to substitute the polynucleotide encoding the p53 protein of Dequiedt et al for the polynucleotide encoding the p53 protein product of US Patent No. 5,532,348 in order to easily produce large quantities of purified p53 product with a conventional method. One of ordinary skill in the art would have had a reasonable expectation of success in producing the product of the combined references.

23. No claims allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 25, 2000